

REMARKS

As correctly stated in the Official Action, Claims 21-25, 27-34, and 45-47 are pending in the present application. Claims 46 and 47 stand withdrawn from consideration. Claims 21-25, 27-34, and 45 stand rejected.

By the present amendment, independent Claims 21, 22, 23, 24, 25 and 45 have been amended to recite "a composition consisting of (i) an effective amount of at least one glucosylated hydroxystilbene compound as the active principle, (ii) one or more usual cosmetic or pharmaceutical additives, and (ii) a physiologically acceptable medium therefor." Support for these amendments can be found, at least, on page 3, lines 1-6 (feature (i)); page 6, lines 23-24 and page 7, lines 1-2 (feature (ii)); and page 7, lines 3-9 (for feature (iii)). Claim 29 has been amended to replace "comprising" with "being selected from the group consisting of." Claims 30 and 31 have been amended to replace "comprising" with "consisting of." New Claims 48-63 derive support from at least, claims 21-25, 45, 27-34, 46, and 47, respectively, and throughout the specification. No new matter has been added. Applicants expressly reserve the right to file a continuation or divisional application on any subject matter canceled by the present amendment.

Rejections Under 35 U.S.C. § 103(a)

Claims 21-25, 27-34, and 45 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Carson et al. (WO 99/047047) and Waterhouse et al. (*Phytochemistry* 37(2):571-573 (1994)). The Examiner argues that Carson et al. disclose that resveratrol is useful in a method of inhibiting the proliferation of keratinocytes and stimulating their

differentiation and improving skin. Further, the Examiner asserts that Carson et al. disclose that compositions containing grape extracts are known in the art. Waterhouse et al. allegedly disclose that resveratrol and piceid (a glycosylated hydroxystilbene) are found in grape extract. Thus, the Examiner concludes it would have been obvious to use grape extracts to treat and improve skin. This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

Carson et al. teach that resveratrol, a phytoestrogen, is useful in methods of inhibiting the proliferation of keratinocytes and stimulating their differentiation, improving the appearance of wrinkled, lined, dry, flaky, aged or photodamaged skin, improving skin thickness, elasticity, flexibility, radiance, glow and plumpness, according to the abstract and Claims 3 and 4. These methods require an amount of from 0.00002 to 10 wt. % of resveratrol, according to Carson et al. Carson et al. also teach that resveratrol is found in a variety of common edible plants, including red grapes. Page 4, line 1 to page 5, line 9 discuss the art known to Carson et al. The only disclosure noted by Carson et al. that mentions any amount of grape to be used for cosmetic purposes is JP 06336421, which teaches the presence of 0.5% of grape extract in its compositions. Carson et al. calculate that this would have a resveratrol concentration of 0.33 micromolar or 0.0000075 wt. %, far below the amount deemed effective by Carson et al.

Although Carson et al. teach that resveratrol can be found in wine and grapes, they do not teach that wine or grape extracts can be applied to the skin to carry out their claimed methods. They teach only that the compound resveratrol itself can be used in their methods. Most importantly, they do not teach that an effective amount of any derivative of

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resveratrol, much less a glucosylated resveratrol, could be used topically to improve the skin conditions according to their invention. Indeed, the Carson et al. reference is silent as to the possibility of using glucosylated resveratrol or any other glucosylated hydroxystilbene in their method.

Waterhouse et al. teach that extracts of grape skin gave a variety of results when the authors analyzed for the presence of resveratrol and piceid, which is 3,4',5-trihydroxystilbene-3- β -mono-D-glucoside. In five different samples from grapes, the following results were obtained: (a) one sample of "Pinot noir" gave the highest level of piceid and no detectable amount of resveratrol; (b) one sample of "Concord" gave no detectable piceid but a detectable amount of resveratrol; (c) one sample of "Syrah" gave 4-5 times as much resveratrol as piceid; (d) one sample of "Pinot noir" gave more than 6 times as much resveratrol as piceid; and (e) one sample of "Pinot noir" gave 15-20% more resveratrol than piceid. As the authors note, they found no proportionality between the levels of resveratrol and those of piceid. Moreover, they admit that they emphasized recovery of piceid over recovery of resveratrol, and further admit that their data are not precise. At any rate, it is apparent from Waterhouse et al. that both piceid and resveratrol can be found in at least some grape/berry skins, while some samples produce no measurable resveratrol and others produce no measurable piceid. The authors suggest on page 572 that the levels of piceid in wine "should be studied to determine whether or not piceid could significantly contribute to the physiologically available pool to humans of resveratrol in wine." This is a suggestion to test wine to see if piceid contributes to the beneficial effects of drinking wine which are noted at the beginning of the Waterhouse et

al. reference. This is a "whether or not"/"if" situation; it is an invitation to investigate or experiment and does not give the ordinary skilled worker a reasonable expectation of success. Furthermore, it does not suggest topical application of wine for any purpose whatsoever, only oral ingestion.

Indeed, the suggestion by Waterhouse et al. that an investigation be conducted into the role of piceid in affecting "the physiologically available amounts of resveratrol to consumers of wine" is made in the context of diseases and biological effects disclosed by those authors. One of the activities noted by Waterhouse et al. is the *in vitro* effect in inhibiting the copper-catalyzed oxidation of low density lipoprotein (LDL), a serum cholesterol fraction. This anti-oxidant effect has been subsequently investigated by Teguo and co-workers for glucosylated and unglucosylated hydroxystilbenes, and their results are reported in Teguo et al., *J. Nat. Prod.* 61, 655-657 (1998). A copy of that publication was earlier made of record by applicants herein together with Applicants' August 15, 2001 Information Disclosure Statement.

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The Teguo et al. publication referred to in the preceding paragraph reports that the glucosylated hydroxystilbenes tested (one of which was piceid) have anti-oxidant activities far inferior to the non-glucosylated hydroxystilbenes tested (one of which was resveratrol). Indeed, the reduction was seven times in the case of (E)-piceid (Compound 3) versus (E)-resveratrol. This is a teaching away from use of glucosylated resveratrol in place of non-glucosylated resveratrol for the biological effects noted by Waterhouse et al. Moreover, as noted above, the Waterhouse et al. reference is silent as to topical application for any purpose whatsoever. Certainly, one of ordinary skill would not be motivated toward

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substituting glucosylated resveratrol for the resveratrol in Carson et al based on the art as a whole, which includes not only Carson et al. and Waterhouse et al. but also Teguo et al. In fact, in light of Teguo et al., applicants' finding that glucosylated hydroxystilbenes can be used to good effect in methods for improving skin conditions as claimed herein is quite surprising.

By the present amendment, independent Claims 21, 22, 23, 24, 25, and 45 have been amended to recite the application of a composition consisting of (i) at least one glucosylated hydroxystilbene compound as the active principle, (ii) one or more usual cosmetic or pharmaceutical additives, and (iii) a physiologically acceptable medium therefor. Thus, the presently claimed invention does not encompass methods using compositions comprising non-glucosylated hydroxystilbenes as disclosed in the Carson et al. and, in particular, grape extract comprising a non-glucosylated form of resveratrol as disclosed in the Waterhouse et al. publication. In this regard, Applicants note that new Claims 48-63 exclude an effective amount of non-glucosylated hydroxystilbenes and thus, are also believed to be unobvious over the cited publications.

It is abundantly clear that applicants' method is not disclosed or suggested by the cited art, taken separately or in combination. Certainly, the prior art references suggest no advantage to combining and modifying them to arrive at applicants' invention. The prior art itself must suggest the reason to combine them (*In re Sernaker*, 217 U.S.P.Q. 1) and indeed it does not. There simply is no basis for combining the cited references, for there is not even an allusion in either one of them for such combination. *United Merchants, etc. v. Ladd*, 139 U.S.P.Q. 199. Further, where references are combined, it should be considered

whether those references suggest doing what applicants did. *In re Gruskin*, 110 U.S.P.Q. 288. The references relied upon here in no way meet that burden. Indeed, the references are silent as to a possible combination and, as was succinctly stated in *In re Burt & Walter*, 148 U.S.P.Q. 548, "Silence in a reference is hardly a proper substitute for an adequate disclosure of facts upon which a conclusion of obviousness may justifiably follow." Also in point as regards the references separately or in combination is *In re Wesslau*, 147 U.S.P.Q. 391, in which the Court stated:

It is impermissible within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such a reference fairly suggests to one of ordinary skill in the art.

In fact, it is only with the benefit of hindsight that one could arrive at applicants' invention and, as the CAFC succinctly put it in *Orthopedic Equipment Co., Inc. v. United States*, 217 U.S.P.Q. 193:

It is wrong to use the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit. Monday morning quarterbacking is quite improper when resolving the question of non-obviousness in a court of law.

When fairly viewed, there is no question but that the cited references simply fail to teach or suggest applicants' invention.

It is clear that the references, separately or in combination, do not suggest using glucosylated hydroxystilbenes in the methods claimed herein. In the case of resveratrol and glucosylated resveratrol, Waterhouse et al show that grape extracts can contain both of these derivatives. Waterhouse et al. also show, however, that grape extracts vary greatly

in their content and that extracts can be obtained which contain no measurable non-glucosylated hydroxystilbenes while other extracts can be obtained which contain no measurable glucosylated hydroxystilbenes. Thus, applicants' method can be readily carried out without using the Carson et al. method which requires resveratrol, even when applicants' glucosylated hydroxystilbenes are derived from wine. It is not applicants' intention to apply the non-glucosylated form in their invention; rather, it is applicants' intention, as discussed in the specification, to use glucosylated hydroxystilbenes, which applicants have found can be converted in the skin or hair follicles to the non-glucosylated hydroxystilbenes and which thus avoid the disadvantages of applying the non-glucosylated hydroxystilbenes themselves directly (also detailed in the specification). The fact that the glucosylated form is converted into the non-glucosylated form in the skin or hair is the discovery of the present inventors that makes the instantly claimed method possible and avoids the disadvantage of direct application of the non-glucosylated compounds.

Moreover, Applicants respectfully submit that the presently claimed invention conveys special advantages in using the glucosylated form of hydroxystilbenes for treating and improving the skin. As discussed in the specification on page 2, lines 21-25 and page 3, lines 1-6, Applicants have surprisingly found that glucosylated hydroxystilbenes can be converted in the skin or hair follicles to non-glucosylated hydroxystilbenes, which enables avoiding the disadvantages (*e.g.*, decreased solubility and stability) of applying non-glucosylated hydroxystilbenes directly.

Applicants respectfully submit that none of the cited publications either separately or in combination, discloses or suggests using glucosylated hydroxystilbenes as the active

principle as in the presently claimed invention, nor is there any motivation to combine the cited publications. Therefore, the cited publications cannot render the presently claimed invention obvious. Additionally, surprising results were obtained with the present invention supporting nonobviousness. Withdrawal of this rejection is respectfully requested.

Note Regarding Claims 46 and 47

On page 2 of the Official Action mailed December 4, 2002, the Examiner argued that claims 46 and 47 were withdrawn as allegedly drawn to a non-elected invention. Applicants stated in their Reply and Amendment filed September 6, 2002, that these claims were encompassed within the scope of Group I (see page 7 of Reply). Moreover, these two claims are dependent upon claim 45, which also falls within the scope of Group I, the elected group. Claims 46 and 47 merely define a further element of an invention recited in Claim 45 that has already been examined. Applicants respectfully submit that claim 45 as discussed above is allowable and thus dependent claims 46 and 47 should also be allowable.

Conclusions

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.


In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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MARKED-UP CLAIMS

21. (Twice Amended) A method for combating signs of cutaneous aging or aging of the hair follicles of an individual subject in need of such treatment, comprising topically applying thereon, for a period of time sufficient to lessen the signs of cutaneous aging or aging of the hair follicles, a composition consisting of (i) an effective amount of at least one glucosylated hydroxystilbene [compound or a composition comprising an effective amount of at least one glucosylated hydroxystilbene] compound as the active principle, (ii) one or more usual cosmetic or pharmaceutical additives and (iii) a physiologically acceptable medium therefor.

22. (Twice Amended) A method for increasing the radiance of the skin of an individual subject in need of such treatment, comprising topically applying thereon, for a period of time sufficient to increase the radiance of the skin, a composition consisting of (i) an effective amount of at least one glucosylated hydroxystilbene [compound or a composition comprising an effective amount of at least one glucosylated hydroxystilbene] compound as the active principle, (ii) one or more usual cosmetic or pharmaceutical additives, and (iii) a physiologically acceptable medium therefor.

23. (Twice Amended) A method for smoothing the facial skin of an individual subject in need of such treatment, comprising topically applying thereon, for a period of time sufficient to elicit a smoothing effect on the facial skin, a composition consisting of (i) an effective amount of at least one glucosylated hydroxystilbene [compound or a

composition comprising an effective amount of at least one glucosylated hydroxystilbene] compound as the active principle, (ii) one or more usual cosmetic or pharmaceutical additives, and (iii) a physiologically acceptable medium therefor.

24. (Twice Amended) A method for treating wrinkles or fine lines in the skin of an individual subject in need of such treatment, comprising topically applying thereon, for a period of time sufficient to lessen the appearance of wrinkles or fine lines in the skin, a composition consisting of (i) an effective amount of at least one glucosylated hydroxystilbene [compound or a composition comprising an effective amount of at least one glucosylated hydroxystilbene] compound as the active principle, (ii) one or more usual cosmetic or pharmaceutical additives, and (iii) a physiologically acceptable medium therefor.

25. (Twice Amended) A method for stimulating epidermal renewal in the skin of an individual subject in need of such treatment, comprising topically applying thereon, for a period of time sufficient to stimulate epidermal renewal in the skin, a composition consisting of (i) an effective amount of at least one glucosylated hydroxystilbene [compound or a composition comprising an effective amount of at least one glucosylated hydroxystilbene] compound as the active principle, (ii) one or more usual cosmetic or pharmaceutical additives, and (iii) a physiologically acceptable medium therefor.

29. (Twice Amended) The method as defined by Claim 45, said at least one glucosylated hydroxystilbene compound [comprising] being selected from the group consisting of 3,4'-dihydroxystilbene-5-O-beta-glucoside; 3,5-dihydroxystilbene-4'-O-beta-glucoside; 4',5-dihydroxystilbene-3-O-beta-glucoside; 4'-hydroxystilbene-3,5-O-beta-diglucoside; 5-hydroxystilbene-3,4'-O-beta-diglucoside; 3-hydroxystilbene-4',5-O-beta-diglucoside; stilbene-3,4',5-O-beta-triglucoside; 4'-methoxy-3',5-stilbenediol-3-O-beta-glucoside; 3,5,4'-trihydroxystilbene-2-O-beta-glucoside; 3',4,5'-trihydroxystilbene-3-O-beta-glucoside; pinosylvin glucoside; 5-hydroxystilbene-3-O-beta-glucoside; 3-hydroxystilbene-5-O-beta-glucoside; and/or stilbene-3,5-O-beta-diglucoside.

30. (Twice Amended) The method as defined by Claim 45, said at least one glucosylated hydroxystilbene compound [comprising] consisting of the D optical isomer thereof.

31. (Twice Amended) The method as defined by Claim 45, said at least one glucosylated hydroxystilbene compound [comprising] consisting of an admixture of glucosylated hydroxystilbene compounds.

45. (Amended) A method for combating signs of cutaneous aging or aging of the hair follicles, for increasing the radiance of the skin, for smoothing the facial skin, for treating wrinkles or fine lines in the skin or for stimulating epidermal renewal in the skin of an individual subject in need of such treatment, comprising topically applying thereon

for a period of time sufficient to lessen signs of cutaneous aging or aging of the hair follicles, to increase the radiance of the skin, to elicit a smoothing effect on the facial skin, to lessen the appearance of wrinkles or fine lines in the skin or to stimulate epidermal renewal in the skin, respectively, a composition consisting of (i) an effective amount of at least one glucosylated hydroxystilbene [compound or a composition comprising an effective amount of at least one glucosylated hydroxystilbene compound] compound as the active principle, (ii) one or more usual cosmetic or pharmaceutical additives, and (iii) a physiologically acceptable medium therefor.